REMARKS

Claims 4, 5, and 7 are pending.

Claim 4 has been amended to rewrite it in independent form, to recite topical administration to the eye, and to recite "c-jun N-terminal kinase inhibitors" instead of "c-jun N-terminal kinase inhibitors and activator protein-1 inhibitors." Claims 1 – 3 and 6 have been cancelled. Claims 5 and 7 have been amended to cause them to depend from Claim 4 instead of Claim 1.

Claims 1 and 7 have been objected to because of informalities. Claim 3 is rejected under 35 U.S.C. 112, second paragraph. Claims 1, 3, and 5 – 7 are rejected under 35 U.S.C. 102(e) as anticipated by Gamache et al. (US 6,696,453). Claims 1, 5 and 6 are rejected under 35 U.S.C. 102(b) as anticipated by Pflugfelder et al. (US 6,153,607). Claims 1 and 2 are rejected under 35 U.S.C. 102(e) as anticipated by Basbaum et al. (US 2002/0151491). Claims 1, 2, and 4 are rejected under 35 U.S.C. 102(e) as anticipated by Graczyk et al. (US 2004/0235864). Claims 1, 6 and 7 are rejected under 35 U.S.C. 103(a) as unpatentable over Pflugfelder (US 6,153,607) in view of de Juan (US 5,980,929). Claims 1, 3, and 5 -7 are rejected under 35 U.S.C. 101 (double patenting) as claiming the same invention as that of Claims 1 – 5 of U.S. Pat. No. 6,696,453.

In order to advance prosecution of this application, Applicant has cancelled Claims 1 – 3 and 6, and rewritten Claim 4 in independent form. Applicant has also amended Claims 5 and 7 to make them dependent from Claim 4 instead of Claim 1. Applicant believes that the Examiner's objections and rejections regarding former Claims 1 – 3 and 5 – 7 are now moot.

Regarding the only rejection applicable to former Claim 4, Applicant notes that the Examiner's basis for the rejection is "Graczyk et al. teach a method of treating dry eye (e.g. also called Sjogren's syndrome, para. 120), using a cytokine synthesis inhibitor, namely c-Jun N-terminal kinase inhibitors (abstract)."

Applicant respectfully traverses this rejection to the extent it may be applied to amended Claim 4. The Graczyk reference discloses certain novel c-jun N-terminal kinase inhibitors and "further provides the use of these compounds in medicine, in particular in the prevention and/or treatment of neurodegenerative disorders related to apoptosis and/or inflammation." Paragraph 120 cited by the Examiner does not disclose or suggest the use of c-jun N-terminal kinase inhibitors for treating dry eye. Instead, paragraph 120 gives a representative listing of the neurodegenerative disorders that the novel reference compounds are particularly useful in preventing or treating. Indeed, the first sentence of paragraph 119 reads: "The compounds of the present invention are particularly useful for the prevention or treatment of a neurodegenerative disorder." Paragraph 119 then goes on to give examples of neurodegenerative disorders (none of which are dry eye). Then paragraph 120 adds that the neurodegenerative disorder may be a peripheral neuropathy. For completeness, Applicant reproduces paragraph 120 below:

> [0120] The neurodegenerative disorder may be a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy. Examples of peripheral neuropathy may be found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystophies, or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple mononeuropathy secondary to sarcoidosis, multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

One skilled in the art reading the disclosure of Graczyk et al. would not conclude that c-jun N-terminal kinase inhibitors would be useful in treating dry eye. Sjogren's syndrome is characterized by activated circulating T-lymphocytes which mediate the disease pathology. Drugs that act by the mechanisms specified in Graczyk et al. can be expected to reduce inflammatory responses of autoreactive T-lymphocytes which invade

the lacrimal gland and reduce tear secretion in Sjogren's syndrome. However, the vast majority of patients with dry eye do not have Sjogren's syndrome or other systemic inflammatory condition. Dry eye is prevalent in otherwise healthy postmenopausal women and in the aging population in general. Other hormonal, anatomical and environmental factors can elicit the signs and symptoms of dry eye in the absence of inflammation. The utility of immunomodulatory or even antiinflammatory therapy in otherwise healthy postmenopausal women and the aging population in general, for example, is not obvious.

Inflammatory factors which mediate ocular surface disease in the majority of dry eye patients are limited predominately to those which can be produced locally by resident ocular surface cells. The disease is established relatively independently of immune cell activation and is not characterized by redness and swelling and pain which classically defines inflammation. Rather, hormonal imbalance or aging can elicit a spectrum of abnormalities in the quantity and integrity of tear components which compromises homeostasis at the ocular surface. Ocular surface cells respond to this stress by secreting proinflammatory cytokines that can adversely affect the function and integrity of a variety of tissue components. Signalling mechanisms which lead to cytokine production in the stressed resident ocular surface cells are different from those that characterize the activation state of recruited or autoimmune inflammatory cells. Also, cytokine secretion profiles of ocular cells differ from that of immune cells. Therefore, the utility of an anti-inflammatory agent acting on cells of the immune system cannot necessarily be anticipated for a disease mediated predominately by resident cells of the eye.

While a symptom of Sjogren's syndrome may be dry eye, Sjogren's syndrome is recognized as an autoimmune disease in which the body's immune system mistakenly attacks its own moisture producing glands. All instances of Sjogren's syndrome are systemic, affecting the entire body. Sjogren's syndrome is also characterized by a number of non-ophthalmic symptoms. See the definition from Stedman's Medical Dictionary (25th Ed), p. 1537, and the description "What is Sjögren's Syndrome?" at http://www.sjogrens.org, both of which are attached hereto.

Even more evidence that the Graczyk et al. reference does not disclose to one skilled in the art that c-jun N-terminal kinase inhibitors are useful in treating dry eye disorders in general can be found by the telling absence of dry eye in the list of "disorders resulting from inflammation" that Graczyk et al. expressly states can be prevented or treated by the reference c-jun N-terminal kinase inhibitors. See paragraph 121 of Graczyk et al:

> [0121] The compounds of the invention can also be used to prevent or treat disorders resulting from inflammation. These include, for example, inflammatory bowel disorder, bronchitis, asthma, acute pancreatitis, chronic pancreatitis, allergies of various types, and possibly Alzheimer's disease. Autoimmune diseases which may also be treated or prevented by the compounds of the present invention include rheumatoid arthritis, systemic lupus erythematosus, glumerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytis anaemia, autoimmune neutropaenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, ulcerative colitis, Crohn's disases, psoriasis or graft vs host disease.

Lastly, Applicant directs the Examiner's attention to paragraph 123 of Graczyk et al. While this reference does mention oral, intravenous, subcutaneous, and intramuscular dosages, there is no mention or suggestion of topical administration of c-jun N-terminal kinase inhibitors to the eye as required by Applicant's claims. This is fully consistent with the fact that one skilled in the art would understand the Graczyk et al. reference to disclose only that certain c-jun N-terminal kinase inhibitors would be useful for treating systemic autoimmune disorders at best, and certainly not topical treatment of dry eye disorders in general.

Applicant believes that the above amendments and remarks have placed Claims 4, 5 and 7 in condition for allowance. Accordingly, allowance of the claims in this application is respectfully requested.

Respectfully submitted,

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9/6/05
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Sézary s., Sézary erythroderma; exfoliative dermatitis with intense pruritus, resulting from cutaneous infiltration by atypical mononuclear cells (T lymphocytes with markedly convoluted or cerebriform nuclei) also found in the peripheral blood, and associated with alopecia, edema, and nail and pigmentary changes; a variant of mycosis fungoides.

Sheehan's s., postpartum pituitary necrosis s.; thyrohypophysial s.; hypopituitarism arising from a severe circulatory collapse postpartum, with resultant pituitary necrosis.

shoulder-girdle s., brachial plexus *neuropathy.*

shoulder-hand s., brachial plexus *neuropathy.*

Shulman's s., eosinophilic *fasciitis.*

Shy-Drager s., a progressive encephalomyelopathy involving the autonomic system, characterized by hypotension, external ophthalmoplegia, iris atrophy, incontinence, anhidrosis, impotence, tremor, and muscle wasting.

sicca s., Sjögren's s.

sick sinus s., chaotic atrial activity characterized by continual changes in P wave configuration, with bradycardia alternating with recurring ectopic beats and runs of supraventricular tachycardia.

Silver-Russell s., Silver-Russell dwarfism; a disorder characterized by low birth weight, late closure of the anterior fontanel, bilateral bodily asymmetry, clinodactyly of the fifth fingers, triangular facies, and carp mouth.

Silverskiöld's s., a type of osteochondrodystrophy with only slight vertebral changes but with shortened and curved long bones of the extremities.

Sipple's s., familial endocrine *adenomatosis,* type 2.

Sjögren's s. [H. S. C. Sjögren], Sjögren's or Gougerot-Sjögren disease; sicca s.; keratoconjunctivitis sicca, dryness of mucous membranes, telangiectasias or purpuric spots on the face, and bilateral parotid enlargement, seen in menopausal woman, and often associated with rheumatoid arthritis, Raynaud's phenomenon, and dental caries; there are changes in the lacrimal and salivary glands resembling those of Mikulicz' disease.

Sjögren-Larsson s., congenital ichthyosis in association with oligophrenia and spastic paraplegia autosomal recessive inheritance.

slit ventricle s., in shunt dependent patients, a state characterized by intermittent or chronic headaches, small ventricles, and slow reflux of the valve mechanism.

Smith-Lemli-Opitz s., mental retardation, small stature, anteverted nostrils, ptosis, male genital anomalies, and syndactyly of the second and third toes, often in breech-born babies with delayed fetal activity.

Smith-Riley s., multiple hemangiomas, macrocephaly, and blurred optic discs; angiomas appear at birth or later, and enlarge and multiply.

smoker's respiratory s., a triad of symptoms seen in smokers, consisting of chronic pharyngitis, wheezing and dyspnea, and a susceptibility to respiratory infections; small lymphoid nodules may appear in the pharynx; there is also often cough, pain in the chest, and hoarseness of the voice; edema of the vocal cords and later an edematous fibroma may be found.

Sneddon's s., a genetic cerebral arteriopathy of unknown etiology, characterized by non-inflammatory intimal hyperplasia of medium-sized vessels associated with diffuse cutaneous livedo reticularis.

Sohval-Soffer s., hypogonadism, gynecomastia, skeletal anomalies, and mental retardation without chromosomal abnormality.

Sorsby's s., congenital macular coloboma and apial dystrophy of the extremities.

Sotos s., cerebral gigantism and generalized large muscles in childhood, with mental retardation and defective coordination; of unknown etiology.

spastic s. in cattle, a disease of the nervous system manifested by spastic contractions of the muscles of one or both hind legs, most common in old bulls; the cramps usually become more frequent and severe, eventually resulting in decreasing the usefulness of the animal.

Spens' s., Adams-Stokes s.

spherophakia-brachymorphia s., Weill-Marchesani s.

splenic flexure s., symptoms of pain, gas, bloating, a sense of fullness experienced in the left upper abdominal quadrant, sometimes beneath the ribs, in some instances radiating upward, and in some instances producing anterior chest pain central or predominantly on the left. It may be induced experimentally by the introduction and trapping of air in the splenic flexure.

Sprinz-Nelson s., Dubin-Johnson *syndrome.*

staphylococcal scalded skin s., Lyell's disease; Ritter's disease (1); a disease affecting infants in which large areas of skin peel off, as in a second-degree burn, as a result of upper respiratory staphylococcal infection even though the skin lesions may be sterile; the level of skin separation is subcorneal, unlike the clinically similar toxic epidermal necrolysis which occurs in children and adults and which involves subepidermal cleavage.

Steele-Richardson-Olszewski s., Steele-Richardson-Olszewski disease; a progressive neurologic disorder in the sixth decade characterized by paralysis of downward gaze rendering ambulation impossible, retraction of eyelids, exophoria under cover, dysarthria, and dementia.

Stein-Leventhal s., polycystic ovary s.

steroid withdrawal s., a condition exhibited by persons who previously had been receiving large therapeutic doses of glucocorticoid hormones for long periods of time; pituitary-adrenocortical insufficiency is manifested, particularly during stress, for as long as a year or more thereafter and varying degrees of emotional disturbance may be exhibited.

Stevens-Johnson s., erythema multiforme bullosum or exudativum; ectodermosis erosiva pluriorificialis; a bullous form of erythema multiforme which may be extensive, involving the mucous membranes and large areas of the body; it may produce serious subjective symptoms and may have a fatal termination. See also ocular-mucous membrane s.

Stewart-Morel s., Morgagni's s.

Stewart-Treves s., angiosarcoma arising in arms affected by postmastectomy lymphedema.

Stickler s., hereditary progressive *arthro-ophthalmopathy.*

stiff-man s., a chronic, progressive, but variable, central nervous system disorder of unknown cause, associated with fluctuating painful muscle spasm and rigidity involving muscles of the limbs, trunk, and neck.

Still-Chauffard s., Chauffard s.

Stockholm s. [*Stockholm,* Sweden, where early case reported], a form of bonding between a captive and captor in which the captive begins to identify with, and may even sympathize with, the captor.

Stokes-Adams s., Adams-Stokes s.

straight back s., loss of the normal anterior concavity of the thoracic spine with resulting compression of the heart between spine and sternum and consequent prominent precordial pulsations, an ejection murmur, and radiologic evidence of a widened cardiac silhouette.

Stryker-Halbeisen s., reddish, scaling, macular eruption on the head and upper trunk due to vitamin B complex deficiency; associated with macrocytic anemia.

Sturge-Kalischer-Weber s., Sturge-Weber s.

Sturge-Weber s., in full, a triad: 1) congenital cutaneous angioma (flame nevus) in the distribution of the trigeminal nerve, usually unilateral; 2) homolateral meningeal angioma with intracranial calcification and neurologic signs; 3) angioma of choroid, often with secondary glaucoma. Incomplete forms of the s. may exhibit any two of the major features in variable degree, occasionally with angiomas elsewhere. Also called cephalotrigeminal or encephalotrigeminal angiomatosis; Sturge-Kalischer-Weber s.; Sturge's or

Stedman's
MEDICAL DICTIONARY

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Sjögren's syndrome is an autoimmune disease in which the body's immune system mistakenly attacks its own moisture producing glands. Sjögren's is one of the most prevalent autoimmune disorders, striking as many as 4,000,000 Americans. Nine out of ten patients are women. The average age of onset is late 40s although Sjögren's occurs in all age groups in both women and men.

About 50% of the time Sjögren's syndrome occurs alone, and 50% of the time it occurs in the presence of another connective tissue disease. The four most common diagnoses that co-exsist with Sjögren's syndrome are Rheumatoid Arthritis, Systemic Lupus, Systemic Sclerosis (scleroderma) and Polymyositis/Dermatomyositis. Sometimes researchers refer to the first type as "Primary Sjögren's" and the second as "Secondary Sjögren's." All instances of Sjögren's syndro are systemic, affecting the entire body.

The hallmark symptoms are dry eyes and dry mouth. Sjögren's ma also cause dryness of other organs, affecting the kidneys, GI tract, blood vessels, lung, liver, pancreas, and the central nervous syster Many patients experience debilitating fatigue and joint pain. Sympt can plateau, worsen, or go into remission. While some people experience mild symptoms, others suffer debilitating symptoms tha greatly impair their quality of life.

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